UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,003	08/15/2006	Ehud Zeigerson	02181.0085U2	1281

23859 7590 12/10/2009

Ballard Spahr LLP
SUITE 1000
999 PEACHTREE STREET
ATLANTA, GA 30309-3915

EXAMINER	
GREENE, IVAN A	
ART UNIT	**PAPER NUMBER**
1619	

MAIL DATE	DELIVERY MODE
12/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,003	ZEIGERSON, EHUD	
	Examiner	Art Unit	
	IVAN GREENE	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *16-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/30/2009 and 10/05/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-41 are currently pending. Claims 16-41 have been withdrawn base upon a restriction requirement discussed below. Claims 1-15 are currently under examination.

Restriction

Applicant's election with traverse of the lack of unity of invention in the reply filed on 10/05/2009 is acknowledged. The traversal is on the ground(s) that the a common technical feature in all of the claims is the use of "a packed bed apparatus under laminar flow conditions". This is not found persuasive because the use of "a packed bed apparatus under laminar flow conditions" would have been obvious over WRIGHT in view of LI and O'HAGAN, as discussed below. Thus, the claims lack unity of invention because they are not so linked as to form a single general inventive concept under PCT rule 13.1. The examiner notes that, upon indication of allowable subject matter, the withdrawn claims will be rejoined as per office practice as stated in MPEP § 821.04.

The requirement is still deemed proper and is therefore made FINAL.

Claims 16-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/05/2009.

Information Disclosure Statement

The information disclosure statement(s) submitted on 03/30/2009 and 10/05/2009 were filed before the mailing date of the first office action on the merits. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the Examiner.

Priority

The U.S. effective filing date for claims 1-13 and 15 has been determined to be 04/10/2003, the filing date of the document 60/461,860. The U.S. effective filing date for claim 14 has been determined to be 04/12/2004 the filing date of the document PCT/US04/11485. The full scope of claim 14 is not supported by the document 60/461,860. No foreign priority has been claimed in the instant application.

Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over WRIGHT (US 6,379,704) in view of LI (US 4,183,681) and O'HAGAN (US 2002/0025329) as evidenced by US 5,733,566.

Applicants Claims

Applicant claims a method of preparing microparticles, comprising the steps of: (a) preparing a first phase, said first phase comprising a solvent, active agent and a polymer; (b) preparing a second phase comprising a solvent; (c) passing said first phase and said second phase through a packed bed apparatus under laminar flow conditions, wherein said method results in the formation of microparticles; and (d) collecting the microparticles containing said active agent. Applicant further claims the packed bed apparatus contains packing material selected from the group consisting of metal, ceramic, plastic and glass. Applicant further claims the first phase (or the second phase) comprising a solvent selected from the group consisting of an organic solvent (methylene chloride, chloroform, ethyl acetate, benzyl alcohol, diethyl carbonate and methyl ethyl ketone) and water. Applicant further claims the emulsion comprises a stabilizer selected from the group consisting of polyvinyl alcohol, polysorbates, protein and polyvinyl pyrrolidone. Applicant further claims the active agent is selected from the group consisting of antioxidants, porosity enhancers, solvents, salts, cosmetics, food additives, textile-chemicals and drugs, inter alia.

Determination of the scope

and content of the prior art (MPEP 2141.01)

WRIGHT teaches a method for preparing microparticles having a selected polymer molecular weight (abstract). WRIGHT further teaches their method comprises the steps of: (a) preparing a first phase, the first phase comprising a nucleophile, a polymer [...] and a solvent for the polymer; (b) *combining the first phase with a second phase under the influence of mixing means to form an emulsion*; (C) combining the emulsion and an extraction medium, thereby forming microparticles [emphasis added] (2:28-35).

WRIGHT teaches the polymers comprising varying lactide:glycolide ratios (3:62-67; 4:1). WRIGHT further teaches example 3 in which the polymer (PLGA MEDISORB® polymers) was dissolved in ethyl acetate to produce a 16.7% w/w polymer solution; the naltrexone [drug active agent] was dissolved in benzyl alcohol to produce a 30.0% w/w solution; the polymer and active agent solutions were then mixed together until a single homogenous solution (organic phase) was produced; the aqueous phase contained 1% w/w polyvinyl alcohol and a saturating amount of ethyl acetate; then these two solutions were pumped via positive displacement pumps at a ratio of 3:1 (aqueous:organic) through a 1/4 [inch] in-line mixer to form an emulsion; and [...] the microparticles were collected on a 25µm sieve and rinsed with a cold (<5˚C) 25% ethanol solution (Example 3, columns 8-9; particularly 8:9-36). The examiner cites US 5,733,566 column 8, lines 18-47 for a more complete description of the MEDISORB® polymers.

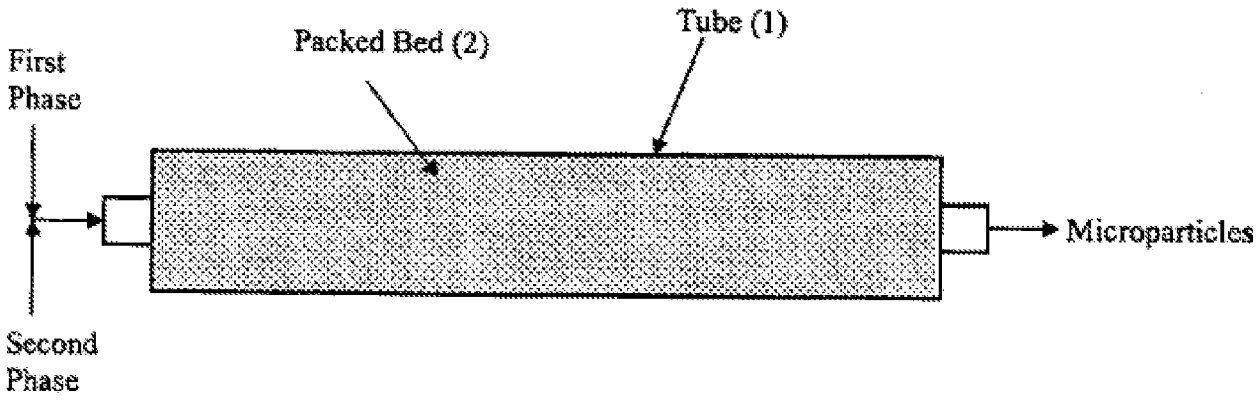
Ascertainment of the difference between

the prior art and the claims (MPEP 2141.02)

The difference between the rejected claims and the teachings of WRIGHT is that WRIGHT does not expressly teach forming an emulsion by passing the phases through a packed bed apparatus under laminar flow conditions. This deficiency in forming an emulsion by passing the phases through a packed bed apparatus under laminar flow conditions is cured by the teachings of LI. O'HAGAN expressly teaches the use of an emulsion stabilizer in the process of forming PLGA microspheres.

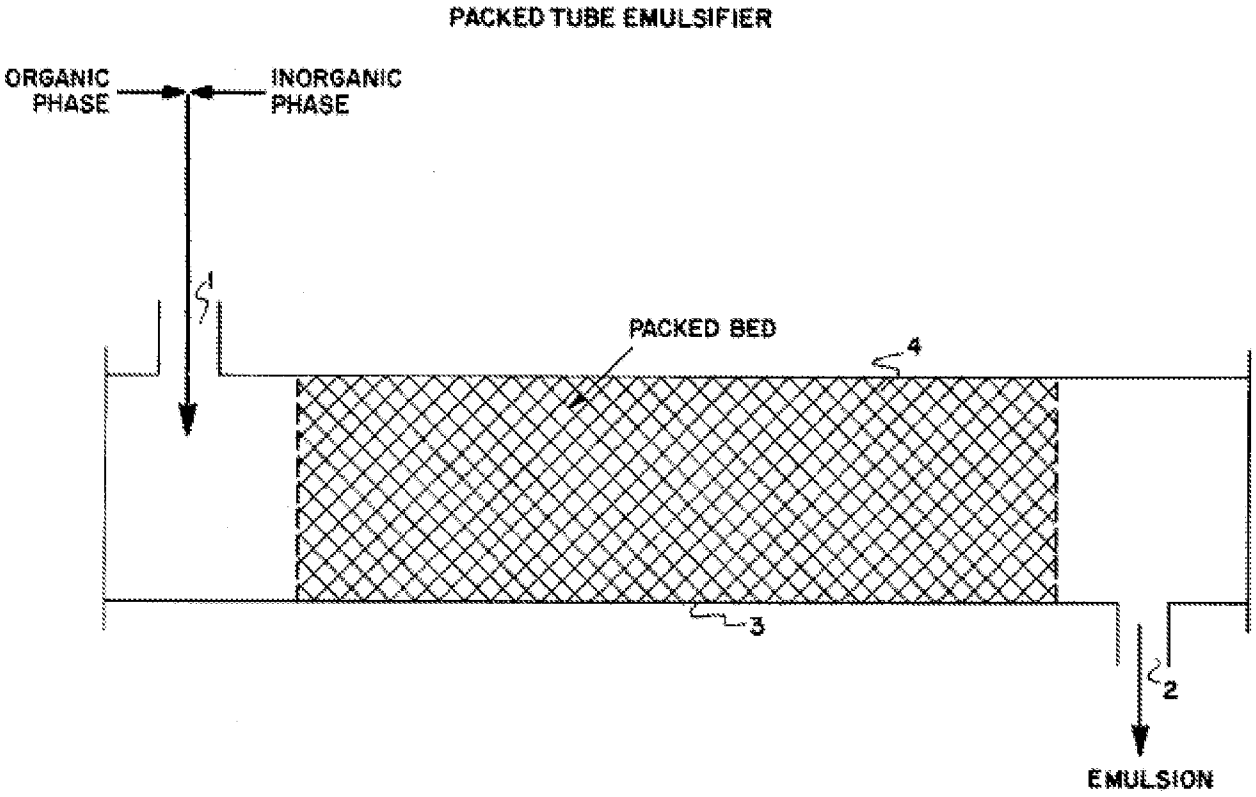
Applicant's specification details the process of forming an emulsion (microparticles) by passing the phases through a packed bed apparatus under laminar flow conditions in figure 1 reproduced below for convenience:

Figure 1 – Packed Bed Apparatus



Li teaches emulsion microparticles (μ-sized droplets) prepared utilizing an emulsification device comprising an enclosure having orifices thereby permitting flow of

a fluid through the enclosure along one of its axis [...] which enclosure is packed with a material which causes the flow of fluids to be broken down into many fine streams, which fine streams being in intimate contact one with the other, remix rapidly and repeatedly, resulting in the formation of the desired emulsion (abstract). Li further detail their process of forming an emulsion (microparticles) by passing the phases through a packed bed apparatus under laminar flow conditions in figure 1 reproduced below for convenience:



LI teaches the arrow pointing into the opening indicates the entrance (1) into which the immiscible fluids are simultaneously introduced for passage through the enclosure (3) to the exit (2), indicated by the arrow pointing away from the enclosure

(3), fluid flow being through the enclosure in the direction resulting from the indicated mode of fluid introduction; the hatching (4) represents the packing filling the enclosure (1:60-68). LI further teaches suitable packing material is selected from the group consisting of steel metal sponge, metal shavings, ceramic chips, Berl Saddle, animal hair or plastic brush, metal tubes shorter than the internal diameter of the enclosure and mixtures of the above (3:12-17). LI further teaches the length of the enclosure from entrance orifices to exit orifices, the amount of packing, the density of the packing, and the type of packing material packed is left to the practitioner, depending on the type of emulsion desired, the density of the fluids used and the final ratio of internal to external phase desired (3:35-40). LI further teaches the fluid feed means are typically selected from the group consisting of pumps for each individual fluid or group of fluids or gravity feed tanks and conduits or syringes for each fluid or group of fluids or any combination of the above (3:43-46). LI further teaches forming different types of emulsions (e.g. water-in-oil, water-in-oil-in-water), [and suggests] many variations in the basic theme can be envisioned and all are included in the scope of their invention (3:49-68). LI further teaches the fluids typically used in preparing a water-oil-water emulsion include an internal water phase wherein is dissolved or suspended any desired material such as medicinal; the oil phase typically comprises and oil component such as petroleum distillate; [and] the oil phase may contain a surfactant (4:1-9). LI teaches the emulsions prepared by the use of the instant apparatus may have droplet size from 0.1μ[m] to greater than 50 μ[m] (4:33-35). The examiner notes, as currently recited, the microparticles of claim 1 read on the micro-sized droplets of LI because no specific

definition for "microparticles" has been provided in the instant specification. And the broadest reasonable interpretation of "microparticles" encompasses micro-sized droplets (see MPEP § 2111 for a discussion of "broadest reasonable interpretation").

O'HAGAN teaches a process for preparing polymer microparticles, similar to WRIGHT, wherein an emulsion stabilizer, such as polyvinyl alcohol or polyvinyl pyrrolidone is used ([0053]).

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the apparatus of LI as a means for forming the emulsion microparticles of WRIGHT and/or O'HAGAN and produces the instantly claimed invention because the apparatus of LI would provide for a continuous emulsion microparticles process. One of ordinary skill in the art would have been motivated to use the apparatus if LI as a means for forming the emulsion microparticles of WRIGHT and/or O'HAGAN because the continuous process would be more efficient, thus saving money.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

2. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over WRIGHT (US 6,379,704) in view of LI (US 4,183,681) and O'HAGAN (US 2002/0025329) and DONOVAN (US 2002/0028216) as evidenced by US 5,733,566, as applied to claims 1-10 and 12-15 above, and further in view of YANAI (US 5,846,562).

Applicants Claims

Applicant claims a method of preparing microparticles, as discussed above. Applicant further claims the emulsion stabilizer is the protein albumin.

Determination of the scope

and content of the prior art (MPEP 2141.01)

WRIGHT teaches a method for preparing a PLGA microparticles emulsion and LI teaches packed tube apparatus for forming an emulsion, as discussed above. O'HAGAN expressly teaches the use of an emulsion stabilizer but does not teach albumin. The difference between the instantly rejected claim and the teachings of WRIGHT, O'HAGAN and LI is that neither WRIGHT, O'HAGAN or LI teach the protein, albumin, as an emulsion stabilizer. This deficiency in the protein, albumin as an emulsifier is cured by the teachings of YANAI.

YANAI teaches their invention relates to a pharmaceutical composition for oral administration in which a fumagillol derivative is stabilized and exhibits remarkable

antiangiogenesis activity in oral administration (abstract). YANAI further teaches the suspension of the present invention comprising the fumagillol derivative oleaginous base and emulsifier, is generally referred to as lipid micro spheres or lipid nanospheres (11:49-52). YANAI further teaches [their composition may include] an emulsion stabilizer for improving the stability of the emulsifying agent which includes albumin, inter alia (12:21-23; 12:45-48).

DONOVAN teaches their invention relates to an implantable drug delivery system including botulinum toxin ([0001]). DONOVAN further teaches albumin has widely been used to improve the stability of microsphere encapsulated protein ([0074]).

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the apparatus of LI as a means for forming the emulsion microparticles of WRIGHT and/or O'HAGAN and produces the instantly claimed invention because the apparatus of LI would provide for a continuous emulsion microparticles process. One of ordinary skill in the art would have been motivated to use the apparatus if LI as a means for forming the emulsion microparticles of WRIGHT and/or O'HAGAN because the continuous process would be more efficient, thus saving money. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use albumin as the emulsion stabilizer in the process for preparing microparticles described by WRIGHT and/or O'HAGAN because

WRIGHT teaches albumin as a suitable emulsion stabilizer. The skilled artisan would have been motivated to use albumin because, as suggested by DONOVAN, the albumin would have improved the stability of microsphere encapsulated protein, thus creating a more valuable product.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

3. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. YANAI (International Journal of Pharmaceutics, 1995, Vol. 123, pp. 237-245), PALM (US 6,140,040) and CATALFAMO (US 6,369,121).

Conclusion

Claims 1-15 have been examined on the merits. Claims 1-15 are rejected under U.S.C. § 103(a). No claims allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to IVAN GREENE whose telephone number is (571)270-

5868. The examiner can normally be reached on Monday through Thursday 7AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bonnie Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

IVAN GREENE
Examiner, Art Unit 1619

/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1619